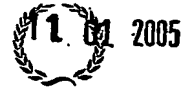




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INVESTOR IN PEOPLE

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1. Your reference

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2. Patent application number

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3. Full name, address and postcode of the or of each applicant (underline all surnames)

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number (if you know it) **00473587003**

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Novel Compounds

5. Name of your agent (if you have one)

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
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980 Great West Road
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Middlesex TW8 9GS

Patents ADP number (if you know it)

08072555004

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 - b) there is an inventor who is named as an applicant, or
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We request the grant of a patent on the basis of this application

Signature

M Gibson

Date 12-Dec-03

12. Name and daytime telephone number of person to contact in the United Kingdom

M Gibson 01279 644841

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NOVEL COMPOUNDS

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β -secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β - amyloid levels or β -amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of A β in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) *Physiological Reviews* **81**: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. β -amyloid (A β) exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) *Neuron* **27**: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) *J. Am. Med. Assoc.* **12**: 1571-1577; Younkin, S. (2001) *Nat. Med.* **1**: 8-19). A β is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β -secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) *Nature* **402**: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of A β peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) *Nature* **402**: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β -secretase) and γ -secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates A β . The non-amyloidogenic, α -secretase pathway, which precludes A β formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α - and β -secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished A β production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) *Nat Neurosci.* **4**: 231-232; Cai, H. *et al.* (2001) *Nat Neurosci.* **4**: 233-234; Roberds, S. L. *et al.* (2001) *Hum. Mol. Genet.* **10**: 1317-1324).

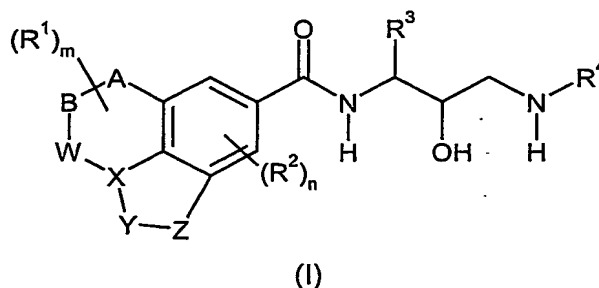
For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally

also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g. Cathepsin D (Connor, G. E. (1998) Cathepsin D in Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woessner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505, WO 02/02506 and WO 03/040096 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β -secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of disease characterised by elevated β -amyloid levels or β -amyloid deposits, such as Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



wherein

R^1 represents C_{1-3} alkyl or halogen;

R^2 represents C_{1-3} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-3} alkoxy, amino, cyano or n hydroxy;

m represents an integer from 0 to 4;

n represents an integer from 0 to 2;

A-B represents $-NR^5-SO_2-$ or $-NR^5-CO-$;

R^5 represents hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl, $-C_{3-10}$ cycloalkyl-aryl or $-C_{3-10}$ cycloalkyl-heteroaryl;

-W- represents $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(H)=C(H)-$ or $-CH_2-C(H)=C(H)-$;

X-Y-Z represents $-C=CR^8-NR^{10a}-$;

R^8 represents hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl;

R^{10a} represents hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl, $-C_{3-10}$ cycloalkyl-aryl, $-C_{3-10}$ cycloalkyl-heteroaryl, $-COOR^{12a}$, $-OR^{12a}$, $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl, $-COC_{3-10}$ cycloalkyl, $-CO$ -aryl, $-CO$ -heteroaryl, $-COC_{1-6}$ alkyl-aryl, $-COC_{1-6}$ alkyl-heteroaryl, $-COC_{3-10}$ cycloalkyl-aryl, $-COC_{3-10}$ cycloalkyl-heteroaryl, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{3-10}$ cycloalkyl, $-SO_2$ aryl, $-SO_2$ heteroaryl,

$-\text{SO}_2\text{C}_{1-6}$ alkyl-aryl, $-\text{SO}_2\text{C}_{1-6}$ alkyl-heteroaryl, $-\text{SO}_2\text{C}_{3-10}$ cycloalkyl-aryl or $-\text{SO}_2\text{C}_{3-10}$ cycloalkyl-heteroaryl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);

R^3 represents optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-\text{C}_{1-6}$ alkyl- C_{3-10} cycloalkyl, $-\text{C}_{1-6}$ alkyl-aryl, $-\text{C}_{1-6}$ alkyl-heteroaryl or $-\text{C}_{1-6}$ alkyl-heterocyclyl;

R^4 represents hydrogen, optionally substituted C_{1-10} alkyl, $-\text{C}_{3-10}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-6}$ alkyl- C_{3-10} cycloalkyl, $-\text{C}_{3-10}$ cycloalkyl-aryl, $-\text{C}_{3-10}$ cycloalkyl-

C_{1-6} alkyl-aryl, -heterocyclyl-aryl, $-\text{C}_{1-6}$ alkyl-aryl-heteroaryl, $-\text{C}(\text{R}^a\text{R}^b)\text{-CONH-}\text{C}_{1-6}$ alkyl, $-\text{C}(\text{R}^a\text{R}^b)\text{-CONH-}\text{C}_{3-10}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl-S- C_{1-6} alkyl, $-\text{C}_{1-6}$ alkyl- NR^cR^d , $-\text{C}(\text{R}^a\text{R}^b)\text{-}\text{C}_{1-6}$

alkyl, $-\text{C}(\text{R}^a\text{R}^b)\text{-}\text{C}_{0-6}$ alkyl-aryl, $-\text{C}(\text{R}^a\text{R}^b)\text{-}\text{C}_{0-6}$ alkyl-heteroaryl, $-\text{C}(\text{R}^a\text{R}^b)\text{-}\text{C}_{0-6}$ alkyl-heterocyclyl, $-\text{C}_{1-6}$ alkyl-O- C_{0-6} alkyl-aryl, $-\text{C}_{1-6}$ alkyl-O- C_{0-6} alkyl-heteroaryl or $-\text{C}_{1-6}$ alkyl-O- C_{0-6} alkyl-heterocyclyl;

R^a and R^b independently represent hydrogen, C_{1-6} alkyl or R^a and R^b together with the carbon atom to which they are attached may form a C_{3-10} cycloalkyl or heterocyclyl

group;

R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a heterocyclyl group;

optional substituents for alkyl groups of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{10a} , R^{12a} , R^{13a} , R^a , R^b , R^c and R^d include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano, hydroxy or $-\text{C}_{1-6}$ alkyl- NR^6R^7 (wherein R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);

and wherein said aryl, heteroaryl or heterocyclyl groups of R^3 , R^4 , R^5 and R^{10a} may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, $-\text{CF}_3$,

$-\text{OCF}_3$, oxo, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, $-\text{NR}^{22}\text{COR}^{23}$, $-\text{CONR}^{22}\text{R}^{23}$ $-\text{C}_{1-6}$ alkyl- $\text{NR}^{22}\text{R}^{23}$ (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl), $-\text{C}_{1-6}$ alkyl-O- C_{1-6} alkyl, $-\text{C}_{1-6}$ alkanoyl or hydroxy groups; or a pharmaceutically acceptable salt or solvate thereof.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkynyl and alkenyl shall be interpreted similarly.

References to C_{3-10} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl which may contain one or more double bonds. When a cycloalkyl group is substituted by two or more C_{1-6} alkyl groups, said cycloalkyl groups together with any two alkyl groups may form a bridged cycloalkyl group which includes bicycloheptyl, adamantyl, bicyclo-octyl and the like.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-10} cycloalkyl fused to a phenyl ring, such as tetrahydronaphthyl).

- References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, tetrazolyl and the like. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.
- References to 'heterocyclyl' include references to a 5-7 membered non-aromatic monocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen and which may contain one or more double bonds. Examples of heterocyclic non-aromatic rings include e.g. morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrazolidinyl and the like.
- Preferably, A-B represents $-NR^5-SO_2-$.
- Preferably, R^5 represents hydrogen, C_{1-6} alkyl (eg. methyl, ethyl or isopropyl), aryl (eg. phenyl) or $-C_{1-6}$ alkyl-aryl (eg. benzyl).
- Preferably, m represents 0 or 1, more preferably 0.
- Preferably, n represents 0 or 1, more preferably 0.
- Preferably, R^8 represents hydrogen.
- Preferably, R^{10a} represents hydrogen or C_{1-6} alkyl (eg. ethyl, propyl or isopropyl), more preferably ethyl.
- Preferably, R^3 represents $-C_{1-6}$ alkyl-aryl (eg. benzyl) optionally substituted by one or two halogen atoms (eg. fluorine or chlorine). More preferably, R^3 represents unsubstituted benzyl.
- Preferably, R^* represents
- C_{1-10} alkyl (eg. 1,5-dimethylhexyl or 1,1,5-trimethylhexyl);
 - C_{3-10} cycloalkyl (eg. cyclopropyl or cyclohexyl);
 - $C(R^aR^b)-C_{0-6}$ alkyl-aryl (eg. benzyl or 1-phenyl-1-methylethyl) optionally
- substituted by one or more halogen, cyano, $-OCF_3$, $-CF_3$, C_{1-6} alkyl or C_{1-6} alkoxy (eg. methoxy) groups;

-C(R^aR^b)-C₀₋₆ alkyl-heteroaryl (e.g. 4-pyrazolyl or 4-thienyl) optionally substituted by one or more halogen, cyano, -OCF₃, -CF₃, C₁₋₆ alkyl (eg. ethyl) or C₁₋₆ alkoxy (eg. methoxy) groups;

- 5 -C(R^aR^b)-CONH-C₃₋₁₀ cycloalkyl (eg. -C(R^aR^b)-CONH-cyclohexyl);
 -C₃₋₁₀ cycloalkyl-aryl; or
 -heterocyclyl (eg. tetrahydropyranyl).

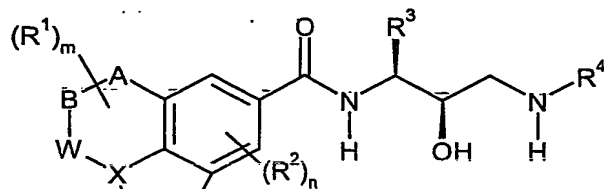
- 10 Preferably, R^a and R^b independently represent hydrogen, methyl or together with the carbon atom to which they are attached form a cyclopropyl or cyclohexyl group, more preferably R^a and R^b both represent hydrogen.

Preferred compounds according to the invention includes examples E1-E5 as shown below, or a pharmaceutically acceptable salt thereof.

- 15 The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic or organic acids e.g.
 20 hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

- 25 The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

- 30 Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any
 35 given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):



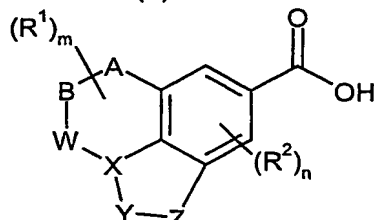
(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

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A process according to the invention for preparing a compound of formula (I) which comprises:

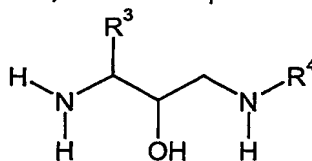
(a) reacting a compound of formula (II)



(II)

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or an activated and/or optionally protected derivative thereof wherein R^1 , R^2 , m , n , A , B , W , X , Y and Z are as defined above, with a compound of formula (III)

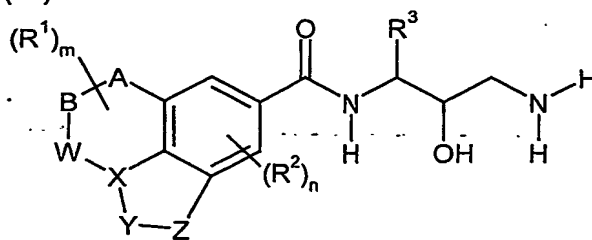


(III)

15

wherein R^3 and R^4 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive alkylation of a compound of formula (IV)



(IV)

20

wherein R^1 , R^2 , R^3 , m , n , A , B , W , X , Y and Z are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Where the compound of formula (II) is an activated derivative, (eg. by activation of a carboxylic acid to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), process (a) typically comprises treatment of said activated derivative with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl. B: The Chemistry of Amides* (Ed. Zabricky, J.) (John Wiley and Sons, 1970), p 73 ff. The acid of formula (II) and amine are preferably reacted in the presence of an activating agents such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT), or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)

Where the compound of formula (II) is a carboxylic acid, process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, eg. between 0°C and room temperature.

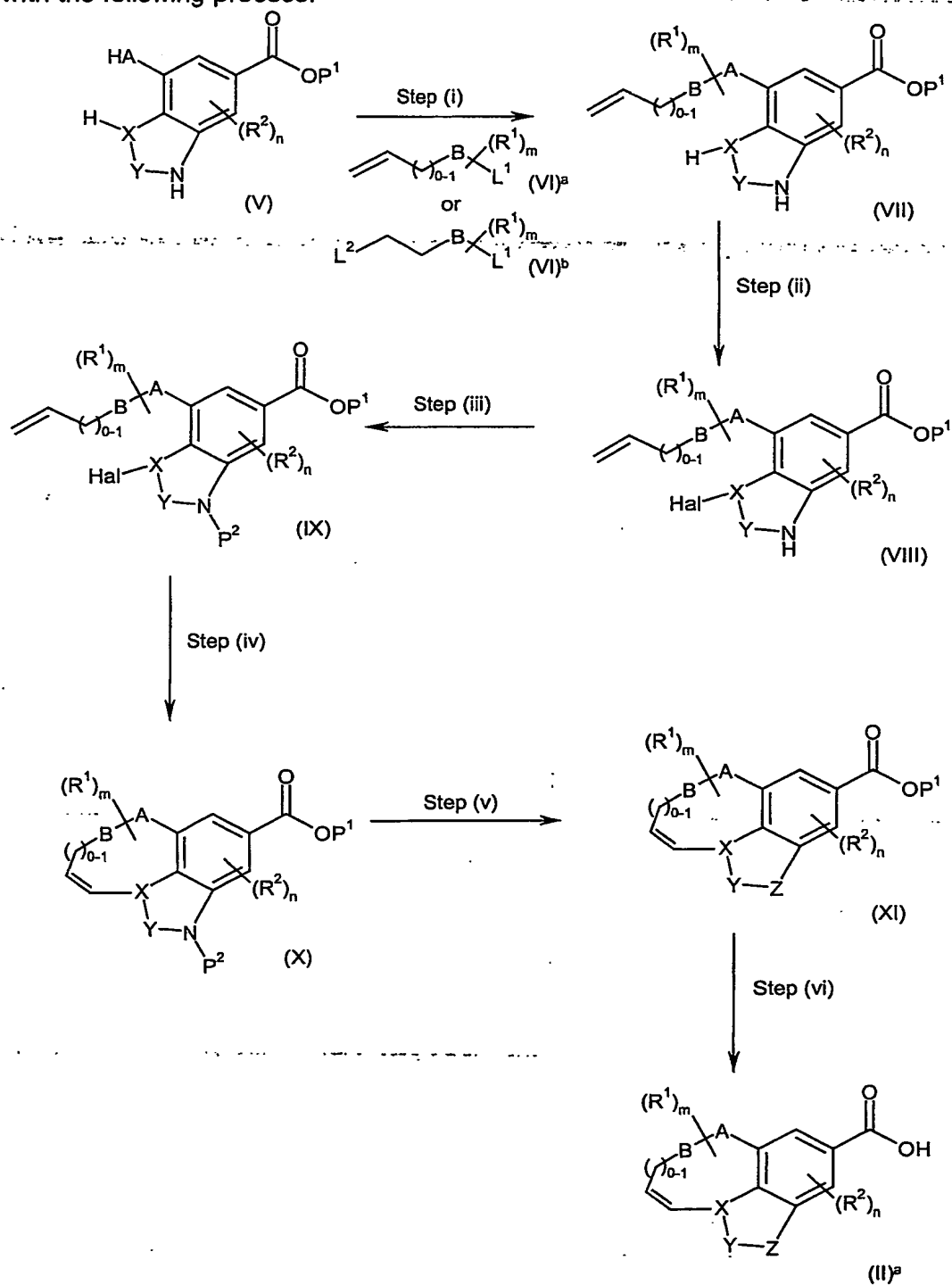
Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol, dichloromethane and 1,2-dichloroethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-COCF₃) which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyltrimethylsilyl, which may be removed using standard methods, for example use of an acid such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation. For example, compounds of formula (I) wherein W represents -C(H)=C(H)- or -CH₂-C(H)=C(H)- may be converted to

compounds of formula (I) wherein W represents $-(CH_2)_2-$ or $-(CH_2)_3-$ by catalytic hydrogenation compounds as herein described.

- 5 Compounds of formula (II) and/or activated and optionally protected derivatives thereof wherein W represents $-C(H)=C(H)-$ or $-CH_2-C(H)=C(H)-$ may be prepared in accordance with the following process:



wherein R^1 , R^2 , m , n , A , B , X , Y and Z are as defined above, P^1 represents a suitable group such as C_{1-6} alkyl, P^2 represents a suitable group such as $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl or $-SO_2$ aryl, L^1 and L^2 independently represent a suitable leaving group such as a halogen atom (eg. chlorine) and Hal represents a halogen atom, such as bromine or iodine.

Step (i) typically comprises reaction of a compound of formula (V) with a compound of formula (VI)^a or (VI)^b in the presence of a suitable base such as pyridine in the presence of a suitable reagent, eg. DMAP and a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature.

Step (ii) typically comprises the use of a halogen such as bromine in the presence of a suitable solvent such as dimethylformamide at a suitable temperature, such as room temperature.

Step (iii) typically comprises introduction of an N-protecting group using standard protocols. For example, an acetate group can be introduced by treatment with acetic anhydride in the presence of a suitable solvent such as pyridine at a suitable temperature, such as room temperature.

Step (iv) typically comprises a standard procedure for addition of a vinyl halide to an alkene, such as the use of a mixture of tetrabutylammonium chloride, palladium acetate and triorthotolyl phosphine in an appropriate solvent such as tetrahydrofuran at an appropriate temperature such as 65°C.

Step (v) typically comprises the use of standard deprotection conditions (e.g. treatment with a suitable amine such as triethylamine in a suitable solvent such as ethanol at an appropriate temperature such as 80°C) and subsequent derivatisation of Z using standard methods (e.g. treatment with a base such as sodium hydride and an alkylating agent such as ethyl iodide in a suitable solvent such as dimethylformamide at an appropriate temperature such as room temperature).

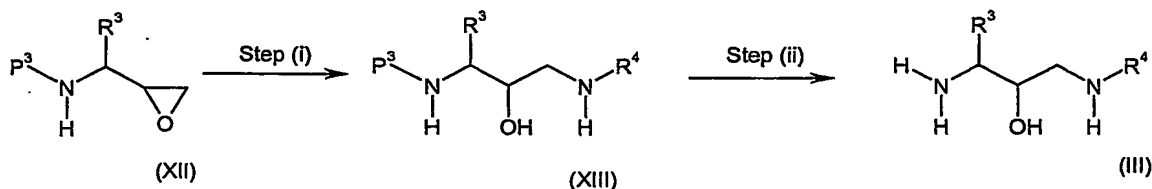
Step (vi) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt like lithium or sodium salt in an appropriate solvent such as methanol at an appropriate temperature such as 50°C. In the case of a tert-butyl ester this conversion can be achieved by the use of an appropriate acid such as trifluoroacetic acid in an appropriate solvent such as dichloromethane at an appropriate temperature such as 0 °C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (II) wherein W represents $-(CH_2)_2-$ or $-(CH_2)_3-$ may be prepared in an identical manner to the process described above except an additional step is required

in which compounds of formula (XI) are hydrogenated prior to step (vi). This step, typically comprises the use of standard reducing conditions such as treatment with 10% palladium on charcoal and ammonium formate in a suitable solvent such as methanol at a suitable temperature e.g. reflux.

5

Compounds of formula (III) may be prepared in accordance with the following process:

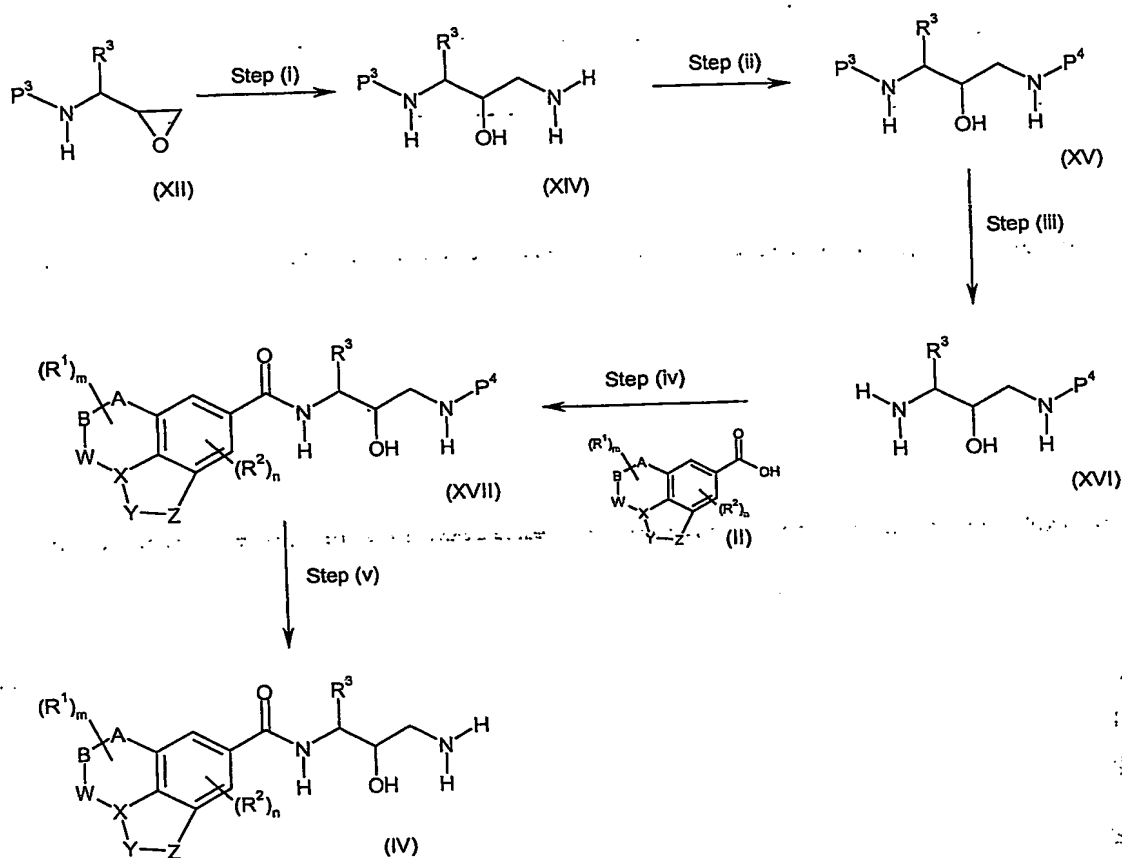


- 10 wherein R³ and R⁴ are as defined above and P³ represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (XII) with a compound of formula NH₂R⁴ in the presence of a suitable solvent, e.g. ethanol at a suitable
 15 temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P³ represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as
 20 dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1 , R^2 , R^3 , m , n , A , B , W , X , Y , Z and P^3 are as defined above and P^4 represents a suitable amine protecting group different to P^3 , such as $-\text{COOCH}_2\text{-phenyl}$.

5

Step (i) typically comprises the reaction of a compound of formula (XII) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

10

When P^4 represents $-\text{COOCH}_2\text{-phenyl}$, step (ii) typically comprises the use of $\text{ClCOOCH}_2\text{-phenyl}$ in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

15

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^3 represents $t\text{-butoxycarbonyl}$, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

20

Step (iv) typically comprises reacting a compound of formula (XVI) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (v) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^4 represents $-\text{COOCH}_2\text{-phenyl}$, deprotection typically comprises the use of a suitable catalyst, eg. palladium in the presence of a suitable solvent, e.g. water and ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, eg. 60°C .

Compounds of formula (V), (VI)^a, (VI)^b and (XII) are either commercially available or may be prepared from commercially available compounds using standard procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β -amyloid levels or β -amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in the therapy of diseases characterised by elevated β -amyloid levels or β -amyloid deposits, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β -amyloid levels or β -amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β -amyloidosis of the Dutch type, cerebral β -amyloid angiopathy and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β -amyloid levels or β -amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents.

Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), gamma secretase inhibitors, anti-inflammatory agents (such as cyclooxygenase II inhibitors), antioxidants (such as Vitamin E and ginkgolides), statins or p-glycoprotein (P-gp) inhibitors (such as cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 and 918).

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil,

fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

- 5 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

10

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form; for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such

- 15 forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into
20 individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

25

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

- 30 The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

35

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

40

Examples

Preparation of Intermediates**Description 1****Methyl 4-methyl-3,5-dinitrobenzoate (D1)**

Thionyl chloride (72 g, 615 mmol) was added dropwise, with stirring, to a suspension of
5 4-methyl-3,5-dinitrobenzoic acid (commercially available from Aldrich)(100 g, 440 mmol)
in methanol (300 ml). The resulting solution was left to stand at room temperature
overnight and the precipitate that formed was then collected by filtration. The filtrate was
washed with cold methanol to give the title compound (D1) as a white solid (104 g, 430
mmol) which was used in the next step without further purification.

10

Description 2**Methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D2)**

A solution of methyl 4-methyl-3,5-dinitrobenzoate (D1) (40 g, 170 mmol) in
dimethylformamide (50 ml) was treated with N,N-dimethylformamide dimethyl acetal (50
15 ml, 380 mmol) and the resulting mixture was heated at 50°C for 1 h. The solvent was
then evaporated and the residue was triturated with diethyl ether/i-hexane (1:1) to give
crude title compound (D2) (40 g, 136 mmol) as a dark red solid. This was used in
subsequent reactions without further purification.

20

Description 3**Methyl 4-amino-1H-indole-6-carboxylate (D3)**

Methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D2) (10.0 g, 34 mmol) in
methanol (150 ml) was treated with ammonium formate (21.4 g, 340 mmol) and wet
(50% water) 10% palladium on carbon (3 g) under a nitrogen atmosphere. The mixture
25 was then heated at 50°C for 1 h. The mixture was filtered and the solvent was removed
by evaporation. The residue was dissolved in ethyl acetate (200 ml) and washed with
saturated aqueous sodium hydrogen carbonate (100 ml). The organic phase was then
dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was
triturated with diethyl ether/i-hexane (1:1) to give the title compound (D3) (5.0 g, 26
30 mmol) as a pale pink solid which was used in subsequent reactions without further
purification. $[M+H]^+ = 191.1$, RT = 2.17 min.

Description 4**Methyl 4-[(ethenylsulfonyl)amino]-1H-indole-6-carboxylate (D4)**

35 To a solution of methyl 4-amino-1H-indole-6-carboxylate (D3)(2.0 g, 10.5 mmol) in
dichloromethane (100 ml) was added triethylamine (2.13 g, 21 mmol) and the mixture
was heated gently to dissolve any remaining solids. 2-chloro-1-ethane sulfonyl chloride
(1.63 g, 10 mmol) was then added dropwise to the mixture and stirring continued for 30
min. At this point a further quantity of 2-chloro-1-ethane sulfonyl chloride (0.39 g, 2.4
40 mmol) was added and stirring continued for a further 30 min. The mixture was washed
sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium
hydrogen carbonate (50 ml) and then the organic phase was dried over magnesium

sulfate, filtered and evaporated *in vacuo*. The residue was triturated with diethyl ether/i-hexane (1:1) to give crude title compound (D4)(1.6 g, 5.7 mmol) as a brown solid which was used in subsequent reactions without further purification. $[M+H]^+ = 281.1$, RT = 2.23 min.

5

Description 5**Methyl 4-[(ethenylsulfonyl)(methyl)amino]-1H-indole-6-carboxylate (D5)**

A solution of methyl 4-[(ethenylsulfonyl)amino]-1H-indole-6-carboxylate (D4)(5.0 g, 17.9 mmol) in dimethylformamide (50 ml) was treated with potassium carbonate (2.48 g, 18 mmol) and iodomethane (1.12 ml, 18 mmol) at room temperature for 90 min. Diethyl ether (200 ml) was added to the mixture and the mixture was then washed sequentially with 2M aqueous hydrogen chloride (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml) and water (3 x 100 ml). The aqueous phase was then dried over magnesium sulfate and then filtered and evaporated *in vacuo* to give the title compound (D5)(4.5 g, 15.3 mmol) as a brown foam. This was used without further purification in subsequent reactions. $[M+H]^+ = 295.1$, RT = 2.48 min.

15

Description 6**Methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1H-indole-6-carboxylate (D6)**

Methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1H-indole-6-carboxylate (D6) was obtained in an analogous manner to that described for the synthesis of (D5) but using iodoethane in the place of iodomethane. $[M+H]^+ = 309.1$, RT = 2.65 min.

20

Description 7**Methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1H-indole-6-carboxylate (D7)**

A solution of methyl 4-[(ethenylsulfonyl)(methyl)amino]-1H-indole-6-carboxylate (D5)(0.700 g, 2.4 mmol) in dimethylformamide (20 ml) was treated dropwise with a solution of bromine (0.12 ml, 2.3 mmol) in dimethylformamide (5 ml) over 15 min. The solvent was then evaporated *in vacuo* and the residue taken up in ethyl acetate (50 ml) and washed with water (2 x 50 ml). The organic phase was then dried over magnesium sulfate, filtered and evaporated to give the title compound (D7)(0.800 g, 2.2 mmol) as a pale brown foam. $[M+H]^+ = 373.0$, RT = 2.74 min.

25

30

Description 8**Methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1H-indole-6-carboxylate (D8)**

Methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1H-indole-6-carboxylate (D8) was obtained in an analogous manner to that described for the synthesis of (D7) but using methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1H-indole-6-carboxylate (D6) in the place of methyl 4-[(ethenylsulfonyl)(methyl)amino]-1H-indole-6-carboxylate (D5). $[M+H]^+ = 389.1$, RT = 2.89 min.

35

40

Description 9

Methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D9)

A solution of methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D7)(0.800 g, 2.2 mmol) in pyridine (5 ml) was treated with acetic anhydride (1 ml, 10.6 mmol) and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (50 ml) and washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate and then filtered and evaporated *in vacuo*. The crude product was recrystallised from ethyl acetate/*i*-hexane to obtain the title compound (D9)(0.510 g, 1.23 mmol) as a pink solid. $[M+H]^+ = 417.0$, RT = 2.85 min.

Description 10

Methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10)

Methyl-1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10) was obtained in an analogous manner to that described for the synthesis of (D9) but using methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D8) in the place of methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D7). RT = 3.01 min

Description 11

Methyl 1-ethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D11)

A solution of methyl-1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10)(0.400 g, 0.94 mmol) in tetrahydrofuran (30 ml) was treated with tetrabutylammonium chloride (0.560 g, 2.0 mmol), palladium diacetate (0.220 g, 1.0 mmol), and triorthotolyl phosphine (0.304 g, 2.0 mmol) under a nitrogen atmosphere. The mixture was heated at reflux for 30 min. The solvent was evaporated and the residue was dissolved in ethyl acetate (100 ml) and washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate and then filtered and evaporated *in vacuo*. The residue was now dissolved in ethanol (50 ml) and treated with triethylamine (0.5 ml, 3.5 mmol). The mixture was then heated at reflux for 15 min before cooling and workup as described above gave the crude product which was crystallised from ethyl acetate/*i*-hexane to give the title compound (D12)(0.280 g, 0.92 mmol) as a brown solid which was used in subsequent reactions without further purification. $[M+H]^+ = 307.1$, RT = 2.54 min

Description 12

Methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12)

Methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12) was obtained in an analogous manner to that described for the synthesis of (D11) but using methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D9) in the place of methyl-1-acetyl-3-bromo-4-

5 [(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10). $[M+H]^+ = 293.1$, RT = 2.37 min

Description 13

Methyl 1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D13)

10 A solution of methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12) (0.400 g, 1.37 mmol) in methanol (50 ml) was treated with ammonium formate (0.800 g, 12.7 mmol) and 10% palladium on charcoal (0.4 g) and the mixture was heated at reflux for 3.5 h. The mixture was then filtered and evaporated *in vacuo*.
15 The residue was dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) then dried over magnesium sulfate. Filtration and evaporation *in vacuo* gave the title compound (D13) (0.220 g, 0.75 mmol) as a brown solid. This was used in subsequent reactions without further purification. $[M+H]^+ = 295.1$, RT = 2.32 min

20

Description 14

[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (D14)

25 ((*S*)-(*S*)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (10 g, 38 mmol) [Chirex 1819W94 Lot#9924382] was dissolved in ethanol (100 ml) and 3-methoxy-benzylamine (14.6 ml, 114 mmol) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in ethyl acetate and washed three times with water, dried over magnesium sulfate and
30 concentrated *in vacuo*. Purification by flash chromatography on silica gel (dichloromethane/methanol: 98/2 to 95/5) gave the title compound (D14) (10.0 g, 66%) as a white solid.

Description 15

35 **1,1-Dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate (D15)**

((*S*)-(*S*)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (1.1 g, 4.1 mmol) [Chirex 1819W94 Lot#9924382] was dissolved in ethanol (100 ml) and tetrahydro-2*H*-pyran-4-ylamine (0.83 g, 8.22 mmol) was added. The resulting mixture was heated,
40 under an atmosphere of nitrogen, for 4 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in ethyl acetate and washed three times with water, dried over magnesium sulfate and

concentrated *in vacuo*. The title compound (D15) was thus obtained as a white solid (0.95 g, 2.6 mmol). $[M+H]^+ = 365.4$, RT = 2.16 min

Preparation of Esters

Ester 1

Methyl 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C1)

A solution of methyl 1-ethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D11) (0.250 g, 0.82 mmol) in dimethylformamide (15 ml) was treated with a 60% suspension of sodium hydride in oil (0.034 g, 0.85 mmol) under an atmosphere of nitrogen. The mixture was stirred for 10 min and then iodoethane (0.156 g, 1.0 mmol) was added and stirring continued for a further 30 min. A further quantity of first sodium hydride (0.034 g, 0.85 mmol) and then iodoethane (0.156 g, 1.0 mmol) were added and the mixture was left to stand overnight. The solvent was evaporated *in vacuo* and the crude title compound (C1) thus obtained was used in the next step without further purification. $[M+H]^+ = 335.2$, RT = 2.83 min

Ester 2

Methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2)

A solution of methyl 1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D13) (0.200 g, 0.68 mmol) in dimethylformamide (15 ml) was treated with a 60% suspension of sodium hydride in oil (0.034 g, 0.85 mmol) under a nitrogen atmosphere and stirred at room temperature for 10 min. The mixture was treated with iodoethane (0.156 g, 1.0 mmol) and stirring was continued for 30 min. The solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate and washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield crude title compound (C2) (0.250 g, 0.78 mmol). This was used without further purification in subsequent reactions. $[M+H]^+ = 323.1$, RT = 2.70 min

Preparation of Acids

Acid 1

6-Ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A1)

To a solution of methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2) (0.250 g, 0.78 mmol) in methanol (20 ml) was added 2N aqueous sodium hydroxide solution (10 ml, 20 mmol). The resulting mixture was heated at 50°C until the solution cleared and then the solvent was evaporated *in vacuo*. The residue was extracted with diethyl ether and then the aqueous layer was acidified using 2M aqueous hydrogen chloride and extracted twice with ethyl acetate.

The ethyl acetate extracts were dried over MgSO_4 , concentrated *in vacuo*, and then triturated with diethyl ether to give the title compound (A1) (0.150 g, 0.49 mmol) as a white solid, which was used in the next step without further purification. $[\text{M}+\text{H}]^+ = 309.1$, RT = 2.33 min

5

Acid 2**1,6-Diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2)**

1,6-Diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2) was obtained in an analogous manner to that described for the synthesis of (A1) but using methyl 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C1) in the place of methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2). $[\text{M}+\text{H}]^+ = 321.2$, RT = 2.45 min

15

Preparation of Bases**Base 1****(2*R*,3*S*)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol di-tosylate (B1)**

To a solution of [(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (D14) (10 g, 25 mmol) in acetonitrile (100 ml) was added *p*-toluenesulfonic acid monohydrate (14 g, 75 mmol) and the resulting mixture was stirred for 16 h. The white precipitate formed was filtered and washed with diethyl ether then dried under vacuum to give the title compound (B1) (15.6 g) as a white solid which was used in the next step without further purification.

25

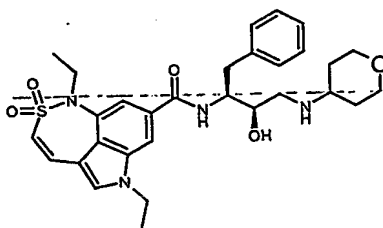
Base 2**(2*R*,3*S*)-3-Amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2)**

(2*R*,3*S*)-3-Amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2) was obtained in an analogous manner to that described for the synthesis of (B1) but using 1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate (D15) in the place of [(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (D14).

35

Examples**Example 1**

1,6-Diethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E1)



To a solution of 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-cd]indole-8-carboxylic acid 2,2-dioxide (A2) (0.038 g, 0.12 mmol) in dimethylformamide (3 ml) was added (2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2) (0.730 g, 0.12 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.030 g, 0.15 mmol), 1-hydroxybenzotriazole hydrate (0.025 g, 0.15 mmol), and triethylamine (0.100 ml, 0.72 mmol). The mixture was stirred overnight at room temperature and then the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated to give the crude product. Purification by biotage (eluting with 2-5% methanol in dichloromethane) and freeze-drying gave the title compound (E1) (0.030 g, 0.05 mmol) as a white solid. $[M+H]^+ = 567.6$, RT = 2.3 min.

Examples 2-4 (E2-E4)

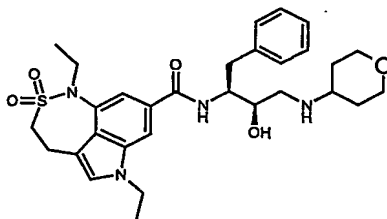
Examples 2-4 were obtained in an analogous procedure to that described for Example 1 using the appropriate acid and the appropriate amine indicated in the table below:

Example	Structure	Acid	Base	$[M+H]^+$	RT (min)
1,6-Diethyl- <i>N</i> -[(1 <i>S</i> ,2 <i>R</i>)-2-hydroxy-3-((3-(methyloxy)phenyl)methyl)amino)-1-(phenylmethyl)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-cd]indole-8-carboxamide 2,2-dioxide (E2)		A2	B1	603.5	2.5
6-Ethyl- <i>N</i> -[(1 <i>S</i> ,2 <i>R</i>)-2-hydroxy-3-((3-(methyloxy)phenyl)methyl)amino)-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-cd]indole-8-carboxamide 2,2-dioxide (E3)		A1	B1	591.5	2.5
6-Ethyl- <i>N</i> -[(1 <i>S</i> ,2 <i>R</i>)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2 <i>H</i> -pyran-4-ylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]		A1	B2	555.5	2.2

thiazepino[5,4,3- <i>cd</i>]indole-8-carboxamide 2,2-dioxide (E4)					
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Example 5

1,6-Diethyl-N-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E5)



A solution of 1,6-diethyl-N-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E1) (0.010 g, 0.02 mmol) in methanol (5 ml) was treated with ammonium formate (0.020 g, 0.32 mmol) and 10% palladium on charcoal (0.015 g) and heated at reflux for 1h. The mixture was filtered and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (30 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated *in vacuo*. Freeze-drying gave the title compound (E5)(0.005 g, 0.01 mmol) as a white solid.

[*M*+*H*]⁺ = 569.6, RT = 2.3 min.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assay:

20 Asp-2 inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-

- a) 1 μ l of a DMSO solution of the test compound (IC₅₀ curve uses ten 1 in 2 serial dilutions from 500 μ M).
- b) 10 μ l of substrate (FAM-[SEVNLDAEFK]-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l), pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.
- c) 10 μ l enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).

Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

The compounds of E1-E5 were tested in the Asp-2 inhibitory assay and exhibited inhibition $<1\mu\text{M}$.

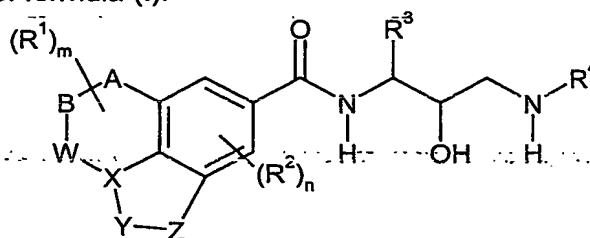
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Abbreviations

	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
10	DMAP	dimethylaminophenol
	DABCO	1,4-diazabicyclo [2.2.2] octane
	DME	dimethyl ether
	THF	tetrahydrofuran
	HOBT	N-hydroxybenzotriazole
15	FAM	carboxyfluorescein
	TAMRA	carboxytetramethylrhodamine
	[]	single amino acid letter code relating to peptide sequence

Claims

1. A compound of formula (I):



(I)

5 wherein

R^1 represents C_{1-3} alkyl or halogen;

R^2 represents C_{1-3} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-3} alkoxy, amino, cyano or n hydroxy;

m represents an integer from 0 to 4;

10 n represents an integer from 0 to 2;

A-B represents $-NR^5-SO_2-$ or $-NR^5-CO-$;

R^5 represents hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl, $-C_{3-10}$ cycloalkyl-aryl or $-C_{3-10}$ cycloalkyl-heteroaryl;

15 $-W-$ represents $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(H)=C(H)-$ or $-CH_2-C(H)=C(H)-$;

X-Y-Z represents $-C=CR^8-NR^{10a}-$;

R^8 represents hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl;

R^{10a} represents hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl, $-C_{3-10}$ cycloalkyl-aryl, $-C_{3-10}$ cycloalkyl-heteroaryl, $-COOR^{12a}$, $-OR^{12a}$,

20 $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl, $-COC_{3-10}$ cycloalkyl, $-CO$ -aryl, $-CO$ -heteroaryl, $-COC_{1-6}$ alkyl-aryl, $-COC_{1-6}$ alkyl-heteroaryl, $-COC_{3-10}$ cycloalkyl-aryl, $-COC_{3-10}$ cycloalkyl-heteroaryl, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{3-10}$ cycloalkyl, $-SO_2$ aryl, $-SO_2$ heteroaryl, $-SO_2C_{1-6}$ alkyl-aryl, $-SO_2C_{1-6}$ alkyl-heteroaryl, $-SO_2C_{3-10}$ cycloalkyl-aryl or $-SO_2C_{3-10}$ cycloalkyl-heteroaryl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);

25 or C_{3-10} cycloalkyl);

R^3 represents optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{1-6}$ alkyl- C_{3-10} cycloalkyl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl or $-C_{1-6}$ alkyl-heterocyclyl;

R^4 represents hydrogen, optionally substituted C_{1-10} alkyl, $-C_{3-10}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkyl- C_{3-10} cycloalkyl, $-C_{3-10}$ cycloalkyl-aryl, $-C_{3-10}$ cycloalkyl- C_{1-6} alkyl-aryl, $-heterocyclyl$ -aryl, $-C_{1-6}$ alkyl-aryl-heteroaryl, $-C(R^aR^b)-CONH-C_{1-6}$ alkyl, $-C(R^aR^b)-CONH-C_{3-10}$ cycloalkyl, $-C_{1-6}$ alkyl-S- C_{1-6} alkyl, $-C_{1-6}$ alkyl- NR^cR^d , $-C(R^aR^b)-C_{1-6}$ alkyl, $-C(R^aR^b)-C_{0-6}$ alkyl-aryl, $-C(R^aR^b)-C_{0-6}$ alkyl-heteroaryl, $-C(R^aR^b)-C_{0-6}$ alkyl-heterocyclyl, $-C_{1-6}$ alkyl-O- C_{0-6} alkyl-aryl, $-C_{1-6}$ alkyl-O- C_{0-6} alkyl-heteroaryl or $-C_{1-6}$ alkyl-O- C_{0-6} alkyl-heterocyclyl;

35 R^a and R^b independently represent hydrogen, C_{1-6} alkyl or R^a and R^b together with the carbon atom to which they are attached may form a C_{3-10} cycloalkyl or heterocyclyl group;

R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a heterocyclyl group;

optional substituents for alkyl groups of R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , R^{10a} , R^{12a} , R^{13a} , R^a , R^b , R^c and R^d include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano, hydroxy or $-C_{1-6}$ alkyl- NR^6R^7 (wherein R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);

and wherein said aryl, heteroaryl or heterocyclyl groups of R^3 , R^4 , R^5 and R^{10a} may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, $-CF_3$,

$-OCF_3$, oxo, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$ $-C_{1-6}$ alkyl- $NR^{22}R^{23}$ (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl), $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, $-C_{1-6}$ alkanoyl or hydroxy groups; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 which is a compound of formula E1-E5 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

4. A compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

5. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the treatment of diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

6. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

7. A method of treatment or prophylaxis of diseases characterised by elevated β -amyloid levels or β -amyloid deposits which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β -amyloid levels or β -amyloid deposits.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP04/014076

International filing date: 09 December 2004 (09.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0328900.6
Filing date: 12 December 2003 (12.12.2003)

Date of receipt at the International Bureau: 04 February 2005 (04.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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